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Diabetes and Pregnancy

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This RISK||NEWSLETTER will focus on the teratogenic effects associated with diabetes. Insulin Dependent Diabetes Mellitus (IDDM) affects 10,000 to 14,000 infants born each year in the United States. Gestational Diabetes (GDM) affects another 100,000 to 140,000 mothers. Various anomalies and risks of birth defects have been associated with each type of diabetes. This RISK||NEWSLETTER will provide an overview on the risks associated with diabetes, on the genetics of the disease, and on options for prenatal diagnosis.

Recent studies have shown that good glycemic control greatly reduces a diabetic woman's risk for congenital malformations. Rosenn and Tsang (1991) summarize several studies with compared incidences of congenital malformations in women with poor versus good control. The rate of birth defects among women with poor control ranges from 4.5% - 35.3%. However, with good glycemic control, these risks are greatly reduced with a range from 0% - 10.7%. Such figures reinforce the importance of establishing preconceptional glycemic control.

Although preconceptional control is universally recognized as a critical factor in diabetic pregnancies, much of the available data on the outcomes of diabetic pregnancies does not specify the degree of glycemic control. Instead, most studies compare diabetic and nondiabetic pregnancies and outcomes without controlling for glycemic status. The statistics in this newsletter are taken from a number of sources with various study methods. Unless otherwise indicated, assume that the studies are comparing diabetic and non-diabetic patients, without separating out women who achieved good preconceptional control.

IDDM

GENERAL INFORMATION

The reported incidence of congenital malformations associated with IDDM varies with different studies. Mills (1988) reports a rate of major malformations 2-3 times greater in infants whose mothers had IDDM at conception. Others have found the rate of anomalies in offspring of diabetic women to be 2-5 times greater than the general population. The overall rate of congenital anomalies in infants born to diabetic mothers may be as high as 10% when there is not good glycemic control. The prevalence of malformations appears to increase with more severe degrees of diabetic disease (Tamura and Dooley, 1991). An assessment of metabolic control is usually based on a measurement of hemoglobin A1C which reflects blood glucose concentrations during the preceding 4-12 weeks. Although the risk for malformation may be increased when hemoglobin A1C is elevated, most fetuses will be normal. Maternal diabetes seems to result in a relatively non-specific effect. Since there has been no demonstrable effect of paternal diabetes, a strong genetic component for anomalies due to diabetes is unlikely (Menutti, 1985).

GENETICS

IDDM is multifactorial in etiology. A multifactorial condition results from the interplay of environmental factors with several genes (polygenic). If a child has IDDM, the risk to his/her siblings is 5-10%. A parent with IDDM has only a 1-2% risk of diabetes developing in his/her offspring during the first decade of life. And, while 1.3% of offspring of diabetic mothers develop IDDM by age 20, 6.1% of offspring of diabetic fathers develop IDDM by this same age (Menutti, 1985).

TIMING OF EXPOSURE

The nature of the defects observed in fetuses of diabetic mothers is indicative of an early embryonic insult. Most of the anomalies in the fetuses of diabetic mothers occur sometimes during the 4th to 7th week of gestation after ovulation. This is a critical period for the teratogenic effect of overt maternal diabetes. It is generally considered that alteration in the maternal metabolic milieu is the most likely explanation for the increased incidence of congenital anomalies in the fetus (Menutti, 1985). Maternal insulin does not cross the placenta. Since insulin from the mother does not reach the embryo during the critical organogenic period, exogenous insulin is not the likely cause of the abnormalities. Fetal insulin is detectable by 10 weeks, well after the critical morphogenic period of most of the pertinent malformations (Grix, 1982). A correlation of malformation incidence with the severity and duration of maternal diabetes suggests that the diabetic process, rather than associated factors, is the causative agent (Barr, 1983).

CONGENITAL ANOMALIES

The most common anomalies in IDDM pregnancies involve the cardiovascular system, the central nervous system (CNS), the genitourinary system, and the face and extremities (Greene, 1991).

Cousins (1991) reported specific abnormalities associated with diabetic pregnancies; these were:

- * CNS: anencephaly, encephalocele, meningomyelocele, spina bifida, and holoprosencephaly
- * Cardiac: transportation of the great vessels, VSD, situs inversus, single ventricle, hypoplastic left ventricle
- * Skeletal: caudal regression
- * Renal: agenesis, multicystic dysplasia
- * GI: anal/rectal atresia, small left colon
- * Pulmonary: hypoplasia

...each group of anomalies will be discussed in detail below.

CENTRAL NERVOUS SYSTEM (CNS)

A 2% risk of neural tube defects (NTD) has been reported in the offspring of diabetic women. This occurrence of NTDs is equivalent to a frequency of about 20/1000 births and represents a 10 fold increase over that in nondiabetic women (Mulunsky, 1982). Menutti (1985) reports an estimated 3-6 fold relative risk for anencephaly, a 3.5-4 fold relative risk for anencephaly with spina bifida, and a 2-2.7 fold relative risk for spina bifida alone. Anencephaly is thought to occur in about 1/200 diabetic pregnancies (Tamura and Dooley, 1991). Barr (1983) reports a risk of 1% for the incidence of holoprosencephaly in the offspring of diabetic women. This makes holoprosencephaly at least 150 times more frequent in the IDDM population. Microcephaly had also been reported to be associated with IDDM, although its etiology is not known.

Due to the greater prevalence of NTD in diabetic pregnancies than in the general population, a number of methods for their early prenatal detection is recommended. Standard procedure for detecting for

NTD is maternal serum alpha-fetoprotein test (MSAFP). If elevated, this screening can be followed by ultrasound evaluation and measurement of alpha-fetoprotein (AFP) and acetylcholinesterase (ACHE) in amniotic fluid (Menutti, 1985). MSAFP must however be modified in diabetic pregnancies because the median value for diabetic women is lower than that for non-diabetic women (Greene, 1991).

CONGENITAL HEART DEFECTS (CHD)

CHD are probably the most prevalent malformation in IDDM (Tamura and Dooley, 1991). Becerra (1990) reports a relative risk of 18 for cardiovascular anomalies associated with IDDM, with an absolute risk of 8.5/100 livebirths. Others report a 2-4 times increased risk for CHD, with the severity and duration of the diabetes impacting on the rate. Rowland et al (1973) found as many as 4% of infants born to diabetic mothers have CHD. Up to 30% of exposed infants have been reported to show asymmetric septal hypertrophy (Cooper et al., 1992). This usually resolves by 1 year of age and is associated with poor control of diabetes during the 3rd trimester. A 20-fold increase in the risk for double outlet right ventricles or truncus arteriosus has also been observed (Ferencz et al., 1990). Greene (1991) and others report that most life threatening heart defects are diagnosable with 2nd trimester echocardiography, although most fetuses with ASD, VSD, and minor heart abnormalities have been missed.

SKELETAL

Although exceedingly rare, caudal regression syndrome is the malformation with the strongest correlation to diabetes (Menutti, 1985). The incidence of the caudal regression syndrome or phocomelic diabetic embryopathy in IDDM is 2-5/1000. This represents a rate 200 times greater than that occurring in the general population. A defect in the embryonic mesoderm during the 4th week of gestation is thought to result in hypoplasia or absence of the caudal structures. It has been suggested that a defect of the midposterior axis mesoderm of the embryo prior to the 5th week of development is the primary error in development leading to the caudal regression syndrome. This mesodermal defect results in fusion of the early lower limb buds with absence or incomplete development of the intervening structures.

ADVERSE ASSOCIATIONS:

Several other anomalies have been reported to be associated with IDDM. Cousins (1991) reports findings of renal agenesis, genitourinary malformation, pulmonary hypoplasia, and a single umbilical artery. Tamura and Dooley (1991) state that IDDM is also associated with polyhydramnios. Dicker (1988) reported that spontaneous abortions have been found in up to 20% of women with IDDM as compared to 15% in the general population, a statistically significant increase. Several other studies could not find an increase in spontaneous abortions among IDDM or gestational diabetics (Kalter, 1987; Crane and Wahl, 1981; Greene et al., 1989). Early growth delay may be important for correlating diabetes control with fetal anomalies (Barr, 1983).

There is need for caution in dating diabetic pregnancies because excessive growth may be detected by ultrasound by the end of the second trimester. The incidence of macrosomia (defined as fetal weight in excess of 4000-4500 grams) has ranged from 16-45% in IDDM pregnancies. Asymmetric macrosomia tends to occur in diabetic patients. In these asymmetric, large for gestational age (LGA) fetuses, the head and femur measurements vary in size and length, but usually fall below the 90th percentile, whereas the abdominal circumference, a measure of fatness, is often greater than the 90th percentile. However, LGA fetuses of diabetic mothers may also have accelerated cephalic growth. IUGR is not common in diabetic pregnancies but is more likely to occur in diabetic pregnancies complicated by vasculopathy (Tamura and Dooley, 1991).

GESTATIONAL DIABETES

2-3% of all pregnancies are associated with gestational diabetes. GDM usually develops during the 2nd to 3rd trimesters and this decreases, but does not completely eliminate, the risk for many of the IDDM-associated malformations. Natural estrogens and progestins facilitate carbohydrate tolerance. Thus it is in the latter pregnancy with the progressive emergence of various events (increased human placental lactogen, increased free cortisol, etc.) that pregnancy becomes “diabetogenic” and GDM is diagnosed. GDM can be defined as the recognition of carbohydrate intolerance (any degree) during pregnancy.

Thus, theoretically, there should, be no risk of congenital defects due to metabolic etiology of GDM. However, any one group of patients with GDM is heterogeneous and it is difficult to distinguish between “true” gestational diabetes and previously asymptomatic diabetes that will persist after pregnancy but was incidentally diagnosed during pregnancy. This latter group is at higher risk for having a baby with congenital malformations, however they cannot be separated out during the course of pregnancy. Therefore, consideration of the heterogeneity of GDM is crucial when studying data regarding these pregnancy outcomes.

For example, Becerra et al., (1990) found that women with GDM who required insulin during the 3rd trimester were at a relative risk of 20.6 for major cardiovascular malformations and an absolute risk of 9.7%. Most commonly occurring were conus arteriosus defects, transposition of the great vessels, PDA, VSD, and pulmonary valve defects. No statistical difference in anomalies was observed among infants of women with gestational diabetes who did not require insulin as compared to controls without any type of diabetes. Hod et al., (1992) performed a case-controlled study that reported increased risk for cardiovascular septation malformation in insulin-dependent GDM, which was not found in GDM patients who did not use insulin. Many other studies did not find increased risks of congenital malformations associated with GDM.

GDM has been associated with an increased risk for poor pregnancy outcome, perinatal mortality, and birth trauma. It has also been associated with increased risk of macrosomia, hypoglycemia, hypocalcemia and hyperbilirubinemia in infants.

PRENATAL DIAGNOSIS

Strict preconceptual metabolic control of diabetes greatly reduces the risk of congenital anomalies associated with diabetes. Steel (1990) reports that preconception glycemic control reduced the risk of birth defects from 10.4% in diabetic women without strict control of glucose levels to 1.4% in a group of women whose levels were strictly regulated. Others have found even lower rates of anomalies. Preconceptional genetic counseling provides patients with information concerning their risks of birth defects and the importance of maintaining good metabolic control. First trimester genetic counseling is useful to describe general population risks, risks screening, and malformations which can be identified.

The most common anomalies in these pregnancies involve cardiovascular system, CNS, genitourinary system, and the face and extremities. Most life-threatening heart defects are diagnosable with 2nd trimester echocardiography. MSAFP screening at 15 weeks provides additional information concerning NTD, detecting 70-80% of fetuses with an open neural tube defects.

The majority of major malformations and other life-threatening defects can be correctly identified by an experienced sonographer before 24 weeks gestation.